

available on PAIR shows that the Amendment was signed. Attached with this Communication is a copy of the signed and dated Amendment.

The Examiner also indicates that claim 27 was presented with the incorrect status identifier. Applicants respectfully assert that claim 27 was amended in Applicants' Amendment of December 14, 2009 and, therefore, was presented with the correct status identifier of "Currently amended."

The Examiner also indicates that claim 27 "has been amended to incorporate the subject matter of non-elected Group IV." Applicants respectfully assert that claim 27, prior to amendment, was the subject matter of Group IV. Claim 27, prior to amendment, was directed to a composition (*i.e.*, the subject matter of Group IV as set forth in the Restriction Requirement dated February 9, 2009). Applicants simply amended claim 27 into a method of use format encompassed by elected Group III. Therefore, Applicants respectfully assert that claim 27, as amended, does not incorporate subject matter of non-elected Group IV. Claim 27, as amended, is encompassed within the elected invention of Group III.

The Examiner further indicates that new claim 29 incorporates non-elected subject matter. Applicants respectfully assert that claim 29 is a method claim dependent from elected claim 17. In addition, claim 29 is generic to the elected species. Therefore, Applicants respectfully assert that claim 29 is part of the elected invention and should be entered and examined in the subject application. If the Examiner disagrees, Applicants respectfully request that the Examiner explain in a further Action the basis as to how claim 29 incorporates non-elected subject matter.

In view of the above, Applicants respectfully assert that the Amendment dated December 14, 2009 is proper and in compliance with the Patent Office's rules concerning Amendments. Accordingly, reconsideration and withdrawal of the Notice of Non-Compliant Amendment, and entry and consideration of the Amendment dated December 14, 2009, is respectfully requested.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this Communication, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachment: Copy of Amendment dated December 14, 2009

I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on December 14, 2009

AMENDMENT UNDER 37 CFR §1.111
Examining Group 1633
Patent Application
Docket No. USF.199TCXZ1
Serial No. 10/567,275


Doran R. Pace, Patent Attorney

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner : Fereydoun Ghotb Sajjadi
Art Unit : 1633
Applicants : M. Ian Phillips, Yao Liang Tang
Serial No. : 10/567,275
Filed : May 9, 2007
Confirm. No. : 9704
For : Stem Cell Beacon

MS AMENDMENT
Commissioner for Patents
P.O. Box 1450
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AMENDMENT UNDER 37 CFR §1.111

Applicants request that the period for response in the above-identified patent application be extended two months through and including December 14, 2009, the fees for which have been paid at the time this Amendment was filed.

In response to the Office Action dated July 14, 2009, please amend the above-identified application as follows:

In the Claims

Claims 1-16 (Cancelled)

Claim 17 (Currently amended): A method of targeting a stem cell to a target tissue in a human or non-human animal subject, the method comprising administering to the target tissue the a composition-of-claim 1 comprising:

(a) a first polynucleotide comprising:

- (1) a gene switch/biosensor comprising a nucleic acid sequence encoding a physiological stimulus-sensitive chimeric transactivator, and
(2) an operatively linked tissue-specific promoter; and

(b) a second polynucleotide comprising a nucleic acid sequence encoding a stem cell-attracting chemokine.

Claim 18 (Previously presented): The method of claim 17, wherein the composition is administered to host cells by a delivery method selected from the group consisting of microinjection, electroporation, calcium phosphate transfection, DEAE dextran transfection, polylysine conjugates, receptor-mediated uptake system, liposomal delivery, lipid-mediated delivery system, matrix-impregnated delivery system, microparticle encapsulation, intra-cellular targeting ligand, virion-like particles, and viral vectors.

Claim 19 (Previously presented): The method of claim 17, wherein the target tissue is selected from the group consisting of heart, bone marrow, blood, brain, blood vessels, spinal cord, peripheral nerve, skeletal muscle, cornea, retina, lungs, liver, and pancreas.

Claim 20 (Previously presented): The method of claim 17, wherein said administering comprises administering the composition to host cells *in vitro* and subsequently administering the host cells to a subject.

Claim 21 (Previously presented): The method of claim 17, wherein said administering comprises administering the composition to cells of the target tissue *in vivo*.

Claim 22 (Previously presented): The method of claim 17, wherein following said administering, the nucleic acid sequence encoding the stem cell-attracting chemokine is expressed in the target tissue, and wherein the chemokine attracts endogenous stem cells or endogenous progenitor cells to the target tissue.

Claim 23 (Previously presented): The method of claim 17, wherein said method further comprises co-administering stem cells to the target tissue.

Claim 24 (Previously presented): The method of claim 17, wherein said method further comprises administering an agent that causes stem cells to migrate to the target tissue.

Claim 25 (Previously presented): The method of claim 17, wherein the target tissue is damaged.

Claim 26 (Previously presented): The method of claim 17, wherein the target tissue is at increased risk of damage.

Claim 27 (Currently amended): A method of targeting a stem cell to a target tissue in a human or non-human animal subject, said method comprising administering to the target tissue a composition comprising:

- (a) a first polynucleotide comprising:
 - (1) a tissue-specific promoter,
 - (2) a nucleic acid sequence encoding a GAL4 DNA-binding domain,
 - (3) a nucleic acid sequence encoding an oxygen-dependent degradation domain (ODD) polypeptide, and

- (4) a nucleic acid sequence encoding a p65 activation domain; and
- (b) a second polynucleotide comprising:
 - (1) at least two copies of a GAL4 upstream activating sequence (UAS),
 - (2) a TATA element, and
 - (3) a nucleic acid sequence encoding a stem cell-attracting chemokine.

Claim 28 (Cancelled)

Claim 29 (New): The method of claim 17, wherein said physiological stimulus-sensitive chimeric transactivator is oxygen-sensitive and comprises a GAL4 DNA-binding domain (DBD), a oxygen-dependent degradation domain (ODD), and a p65 activation domain (p65 AD); and wherein said second polynucleotide further comprises a GAL4 upstream activating sequence (UAS) linked to said nucleic acid sequence of said second polynucleotide, and wherein in response to hypoxia, said transactivator binds to the GAL4 UAS, resulting in expression of said nucleic acid sequence encoding said stem cell-attracting chemokine.

Claim 30 (New): The method of claim 17, wherein said tissue-specific promoter is specific for expression in a tissue selected from the group consisting of kidney, epithelial tissue, endothelial tissue, liver, brain, neural tissue, thymus, and pancreas.

Claim 31 (New): The method of claim 17, wherein said tissue-specific promoter is selected from the group consisting of CLCN5, rennin, androgen-regulated protein, sodium-phosphate cotransporter, renal cytochrome P-450, parathyroid hormone receptor, kidney-specific cadherin, E-cadherein, estrogen receptor (ER) 3, endoglin, ICAM-2, human phenylalanine hydroxylase (PAH), human C-reactive protein (CRP), human enolase (ENO3), thy-1 antigen, gamma-enolase, glial-specific glial fibrillary acidic protein (GFAP), human FGF1, GATA transcription factor, and pancreas duodenum homeobox 1 (PDX-1).

Claim 32 (New): The method of claim 17, wherein said tissue-specific promoter is a cardiac-specific promoter.

Claim 33 (New): The method of claim 17, wherein said tissue-specific promoter is a cardiac-specific promoter selected from the group consisting of the ventricular form of the MLC-2v promoter, a fragment of the native MLC-2v promoter, alpha myosin heavy chain promoter, and myosin light chain-2 promoter.

Claim 34 (New): The method of claim 17, wherein said stem cell-attracting chemokine is selected from the group consisting of SCF, vascular endothelial growth factor (VEGF), granulocyte colony-stimulating factor (G-CSF), an integrin, and hSDF-1alpha.

Claim 35 (New): The method of claim 17, wherein said stem cell-attracting chemokine comprises hSDF-1alpha.

Claim 36 (New): The method of claim 17, wherein said physiological stimulus is associated with cell injury.

Claim 37 (New): The method of claim 17, wherein said physiological stimulus-sensitive chimeric transactivator is sensitive to hypoxia or an elevated glucose level.

Claim 38 (New): The method of claim 17, wherein the stem cell attracted by said stem cell-attracting chemokine is from an anatomical site selected from the group consisting of bone marrow, peripheral blood, brain, spinal cord, dental pulp, blood vessels, skeletal muscle, epithelia of the skin, epithelia of the digestive system, cornea, retina, liver, and pancreas.

Claim 39 (New): The method of claim 17, wherein said composition is a recombinant viral vector.

Claim 40 (New): The method of claim 17, wherein said composition is a recombinant viral vector selected from the group consisting of an adenovirus, an adeno-associated virus, a herpes simplex virus, a lentivirus, and a retrovirus.

Claim 41 (New): The method of claim 17, wherein said composition is a recombinant adeno-associated viral vector.

Claim 42 (New): The method of claim 17, wherein said composition is a non-viral vector.

Claim 43 (New): The method of claim 17, wherein said composition is a plasmid.

Claim 44 (New): The method of claim 17, wherein said method further comprises co-administering to the target tissue stem cells and an agent that causes stem cells to migrate to the target tissue.

Remarks

Claims 1-28 were pending in the subject application. By this Amendment, claims 17 and 27 have been amended, claims 1-16 and 28 have been cancelled, and new claims 29-44 have been added. Support for the new claims and amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 17-27 and 29-44 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Claim 17 is objected to on the grounds that it refers back to a withdrawn claim. By this Amendment, Applicants have amended claim 17 to delete the reference back to claim 1 and to specifically recite the text of claim 1 in claim 17. Accordingly, reconsideration and withdrawal of this objection is respectfully requested.

Claims 17-22 and 24-26 are rejected under 35 USC §103(a) as obvious over Petersen (U.S. Patent Publication No. 2002/0094327) in view of Phillips *et al.* (2002) and in further view of Tang *et al.* (2002). In addition, claims 17 and 23 are rejected under 35 USC §103(a) as obvious over Petersen (U.S. Patent Publication No. 2002/0094327) in view of Phillips *et al.* (2002) and Tang *et al.* (2002), further in view of Kovesdi *et al.* (U.S. Patent Publication No. 2003/0027751). The Examiner asserts that the Petersen publication teaches a method of modulating the targeting of pluripotent stem cells to a target tissue of a mammalian subject by increasing the concentration of SDF-1 alpha protein in the target tissue. The Examiner asserts that the Phillips *et al.* publication teaches a vigilant vector comprising a heart-specific promoter (MLC2v) operably linked to a hypoxia response element and a therapeutic gene in an AAV vector, for cardioprotection. The Phillips *et al.* and the Tang *et al.* publications are both cited as teaching a double plasmid approach that produces a powerful chimeric transcription factor consisting of the yeast transcription factor GAL4 DNA binding domain and the p65 transactivation, that when combined with HRE and SV40 promoter, increased gene expression 400-fold when activated by hypoxia. The Kovesdi *et al.* reference is cited as teaching vectors encoding VEGF administered to cardiac tissue and co-administered with factors (such as GM-CSF) and stem cells. The Examiner concludes that it would have been obvious for a person of ordinary

skill in the art at the time of the subject invention to combine the teachings of the cited references and to substitute the SDF-1 alpha gene taught by Petersen for the therapeutic gene of Phillips *et al.* Applicants respectfully traverse these grounds of rejection.

Applicants respectfully assert that the cited references, taken alone or in combination, do not teach or suggest the claimed invention. As the Examiner is aware, in order to support a *prima facie* case of obviousness, a person of ordinary skill in the art must generally find both the suggestion of the claimed invention, and a reasonable expectation of success in making that invention, solely in light of the teachings of the prior art and from the general knowledge in the art. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). One finds neither the suggestion, nor the reasonable expectation of success, of Applicant's claimed invention in the cited references.

Applicants note that the cited references were all published at about the same time (*i.e.* 2002). However, the Petersen reference does not teach or suggest anything related to the vectors disclosed in the Phillips *et al.* and Tang *et al.* references. If it was so obvious to a skilled artisan to combine the teachings of the cited references, then one would expect that Petersen or another skilled artisan would have published such a disclosure soon after the publication of the cited references, yet the Examiner has not cited any such references. The Phillips *et al.* and Tang *et al.* references may disclose a gene switch for injection directly into the heart. However, the disclosure in the Phillips *et al.* and Tang *et al.* references does not teach or suggest anything regarding stem cells. Thus, Applicants maintain that their claimed invention was not obvious over the cited references.

Applicants respectfully assert that, in addition to the fact that the cited references do not teach or suggest the claimed invention, the cited references also do not provide a reasonable expectation of success in arriving at Applicants' claimed invention. Applicants are the authors of the Phillips *et al.* and Tang *et al.* references and respectfully submit that it took a considerable amount of time and continuous experimentation to conceive and develop the claimed invention. Applicants note that the cited Phillips *et al.* and Tang *et al.* references have a publication date in 2002. The earliest priority date of the subject application is August 2003. Thus, at least several months of empirical research and development were required by Applicants after the publication of the Phillips *et al.* and Tang *et al.* references in order to arrive at the claimed invention of the subject application.

Applicants respectfully assert that it cannot be predicted that vector systems such as that of the invention will be effective in the intended physiological environment without at least some empirical work providing proof of principle. It was not obvious that an SDF-1 gene could be included in the vector construct of the invention without verifying that the gene could fit in the construct and achieve an effective level of protein expression. The inventors had to empirically determine goodness of fit and the amount of SDF-1 gene expression for a given degree of oxygen deprivation. Furthermore, the inventors had to determine whether tissue-specific promoters were sufficiently powerful to drive expression of SDF-1 so as to be effective *in vivo*. Vector systems must be designed and tested *in vitro* and *in vivo*. As indicated at page 654, second column, of the Phillips *et al.* reference, "basal levels, times of response, tissue specificity, and amplification of signals are all challenges to be met". Moreover, the ability of SDF-1 to attract cardiac stem cells was not known in the art at the time of the present invention, and is particularly advantageous for treatment of cardiovascular pathologies since endogenous cardiac stem cells are probably the most appropriate cell source for use in cardiac repair.

In view of the above remarks, reconsideration and withdrawal of the rejections under 35 USC §103(a) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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